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Amination/Cyclization Cascade by Acid-Catalyzed Activation of Indolenine for the One-Pot Synthesis of Phaitanthrin E

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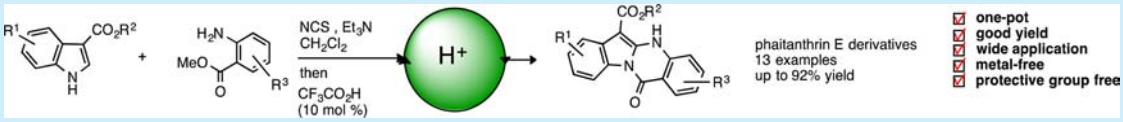
Supporting Information



ABSTRACT: We have developed a concise one-pot synthesis of phaitanthrin E derivatives, where simple starting materials undergo an acid-catalyzed intermolecular amination/intramolecular cyclization cascade.

Indolo[2,1-*b*]quinazoline alkaloids have attracted considerable interest because of their intriguing tetracyclic core and wide range of promising biological activities.[1] Five new alkaloids, phaitanthrin A (**1**), B (**2**), C (**3**), D (**4**), and E (**5aa**), were isolated from *Phaius mishmensis* (Orchidaceae) by Wu and co-workers (Figure 1).[2] In 2013, Vaidya and Argade[3]

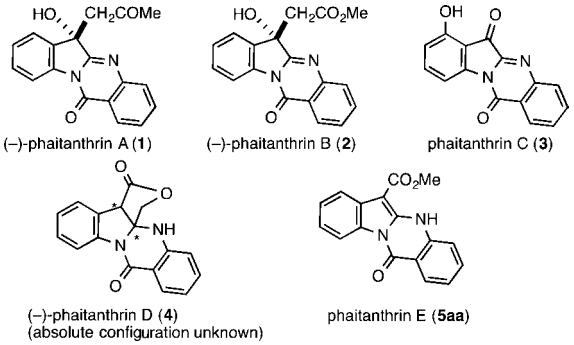


Figure 1. Phaitanthrins A–E.

reported the synthesis of (±)-**2** and **3** through an aryne insertion reaction. Recently, the enantioselective synthesis of **1** and **2** was accomplished by Jiang's group.[4] In 2015, the first elegant total synthesis of (±)-**4** and **5aa** via intramolecular dehydrative cyclization of anthranilamide involving unusual C_{sp^3}–C_{sp^3} bond activation was accomplished by Vaidya and Argade.[5] Very recently, the first synthesis of (−)-**4** from a pivotal enantiomerically pure anthranilamide was also reported.[6] We previously reported the one-pot synthesis of tryptanthrin by oxidative dimerization of indoles[7] and the one-pot synthesis of **5aa** from methylindole 3-carboxylate and isatoic anhydride through a Cu-mediated intermolecular condensation/intramolecular aryl C–H amination cascade.[8] However, this cascade for the synthesis of **5aa** did not exhibit good functional group tolerance and scalability because of the harsh reaction conditions employing stoichiometric copper complexes. Therefore, we next set out to develop an efficient synthesis of **5** under mild reaction conditions.

Cascade reactions play an important role in total synthesis and biogenesis.[9] Although C-2 amination/cyclization on the indole nitrogen could be the most rapid formation of polyheterocycles, the precedents are rare. Moreover, electrophilic C-2 transformations of indoles have been limited to intramolecular reactions because of the high nucleophilicity at C-3, leading to C-2/C-3 dimerization.[10] Herranz demonstrated the use of nitrile protonation of tryptophan-derived α-amino nitrile **6** in the synthesis of tetracyclic heterocycle **7** (Scheme 1a) via a cascade sequence proceeding through intramolecular amination at C-2 of the indole ring followed by intramolecular cyclization at the nitrogen atom of the indole ring.[11] Recently, Roche developed an elegant double annulative cascade reaction of tryptophan-containing peptide **8** initiated by fluorine-mediated dearomatization (Scheme 1b).[12] This cascade sequence is efficient in building the stereochemically dense tetracyclic α-carboline **9**.

On the basis of our continuous efforts on the synthesis of polycyclic heterocycles[13] and the above acid-mediated domino syntheses (Scheme 1a,b), herein we report a novel cascade sequence starting from methyl indole-3-carboxylate (**10a**) and methyl anthranilate (**11a**) to afford tetracyclic heterocycle **5aa** initiated by the combination of chlorine-mediated dearomatization/acid-catalyzed protonation of indolenine (Scheme 1c). This reaction proceeds through intermolecular amination of indolenium ion **12**/intramolecular cyclization of intermediate **13**/aromatization in a single step. Although the approaches of Herranz and Roche are intramolecular strategies using complicated compounds obtained by multistep syntheses, our approach is an intermolecular one-pot approach using simple starting materials, thus offering a straightforward and efficient entry to tetracyclic heterocycles.

Initially, we began our experiment with indole **10a** and anthranilate **11a** and used acid catalysts to obtain **5aa** (Table 1). A preliminary attempt with NCS (1.1 equiv), Et_3N (2 equiv), and AcOH (10 mol %) in CH_2Cl_2 at room temperature

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Scheme 1. Synthesis of Polycyclic Indole Compounds via Amination/Cyclization Cascade

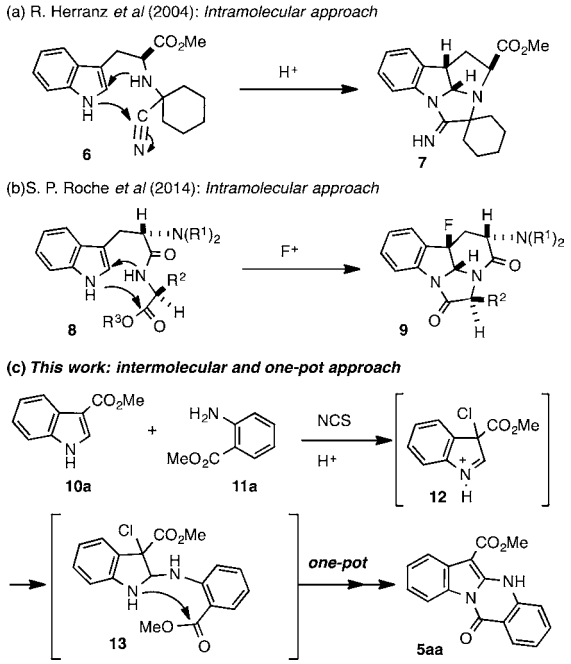
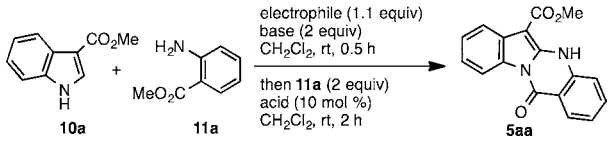


Table 1. Optimization of the Reaction Conditions[a]



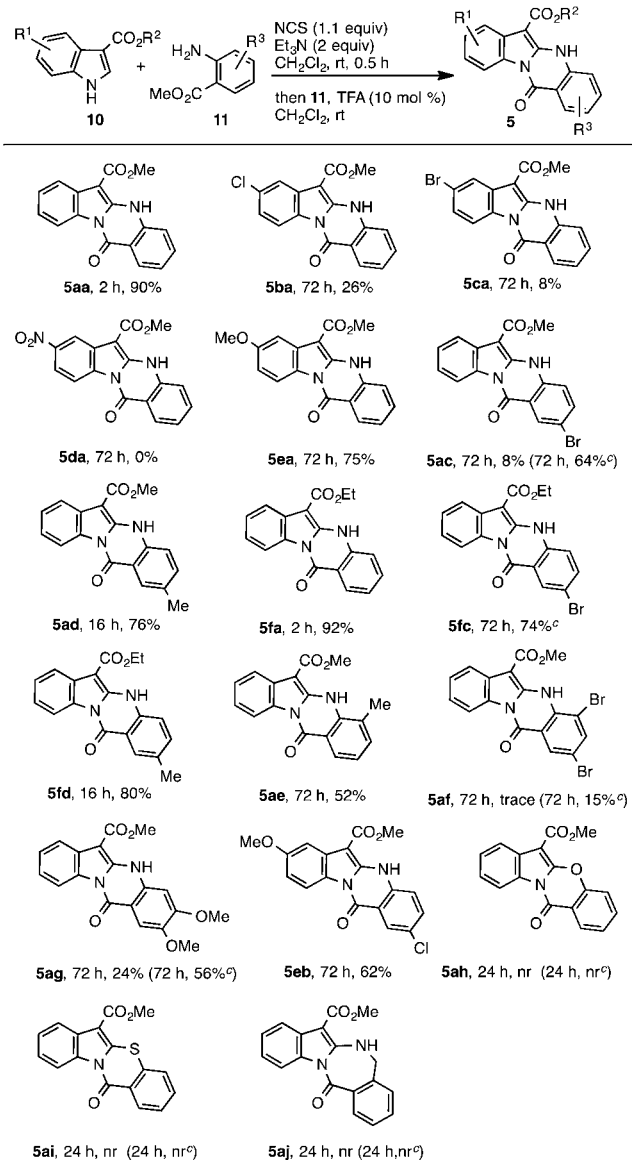
run	acid	electrophile	base	yield (%)[b]
1	AcOH	NCS	Et_3N	5
2	conc. HCl	NCS	Et_3N	84
3	H_2SO_4	NCS	Et_3N	82
4	$MeSO_3H$	NCS	Et_3N	55
5	CCl_3CO_2H	NCS	Et_3N	52
6	TFA	NCS	Et_3N	90
7	TFA	NFSI	Et_3N	0
8	TFA	NBS	Et_3N	0
9	TFA	NIS	Et_3N	0
10	TFA	NCS	pyridine	0
11	TFA	NCS	DMAP	0
12	TFA	NCS	iPr_2NEt	8
13	TFA	NCS	Et_2NH	0
14	TFA	NCS	DBU	45
15	TFA	NCS	DABCO	74
16	TFA	NCS	NaOH	0
17	TFA	NCS	K_2CO_3	5

[a]**10a** (1 mmol), **11a** (2 mmol), acid (10 mol %), electrophile (1.1 mmol), and base (2 mmol) in CH_2Cl_2 (10 mL). [b]Isolated yields.

led to the desired product **5aa** in only 5% yield (entry 1). Probing different acid catalysts suggested the acidity of the catalyst to be of key importance, and TFA was found to be the best catalyst (entries 2−6). Replacing NCS with *N*-fluorobenzenesulfonimide (NFSI), NBS, or NIS resulted in no product (entries 7−9). In the case of NBS, indole-3-carboxylate acts as an efficient bromine source in the combination of NBS.[14] Therefore, no haloindolenium ion was generated, resulting in no reaction. Among various bases screened, Et_3N was the most effective (entries 10−17). When inorganic bases such as NaOH and K_2CO_3 were used in place of Et_3N, this cascade reaction was not operative because the acid catalyst was neutralized. In contrast, organic bases would form the ammonium salts, which might act as a catalyst. The details are not clear and are under investigation.

Next, we investigated the scope of substrates in the cascade sequence under the optimized conditions (Scheme 2). The

Scheme 2. Substrate Scope of Indoles and Anthranilates[a,b]



[a]**10** (3 mmol), **11** (6 mmol), TFA (10 mol %), electrophile (3.3 mmol), and Et_3N (6 mmol) in CH_2Cl_2 (25 mL). [b]Isolated yields are shown. [c]K_2CO_3 was added to the mixture at rt, and the mixture was stirred for 16 h.

presence of electron-withdrawing or -donating groups at C-5 of the indole ring led to a decrease in the yield (**5ba**, **5ca**, and **5ea**). No product could be obtained when methyl 5-nitroindole-3-carboxylate was used (**5da**). The use of an electron-withdrawing group at C-5 of the anthranilic acid resulted in a decreased product yield (**5ac**). We suspect that the substituted group at methyl anthranilate inhibits the cyclization

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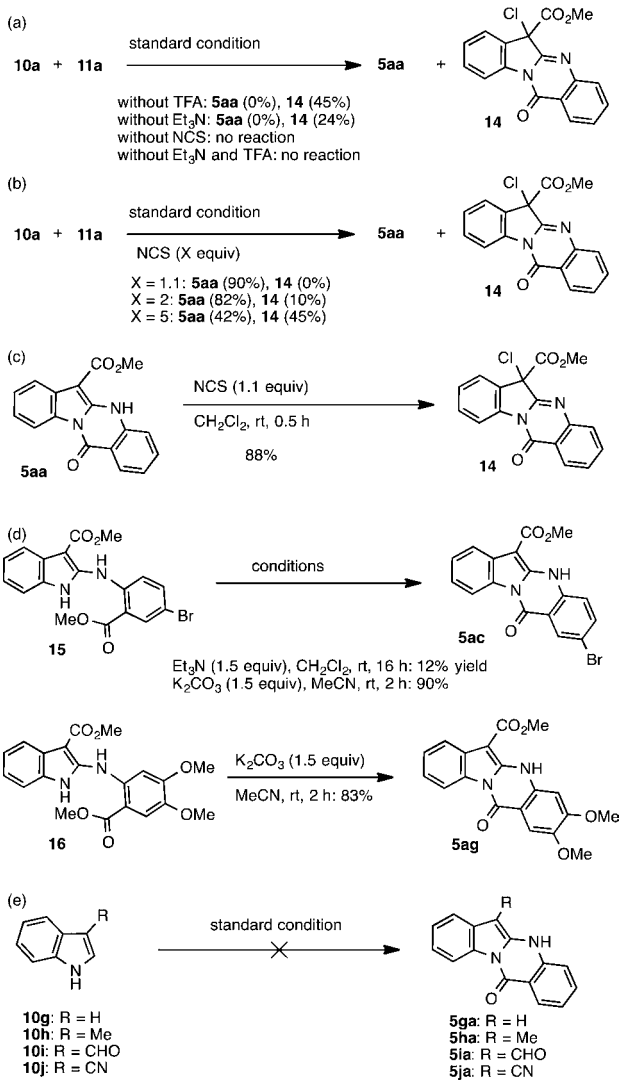
step. To promote the cyclization, the use of an additional base was also attempted. Fortunately, K_2CO_3 as an additional base enabled cyclization to occur, affording **5ac** in 64% yield. Indoles bearing an ethyl ester could be also used in the cascade sequence (**5fa**, **5fc**, and **5fd**). Further substitution around the aniline ring was also tolerated (**5ae**, **5af**, and **5ag**). The use of both substituted indole and substituted anthranilate was also applicable for the cascade (**5eb**). To broaden the scope of nucleophiles, other nucleophiles such as methyl salicylate, methyl thiosalicylate, and methyl 2-aminomethylbenzoate were also tested (**5ah**, **5ai**, and **5aj**). Unfortunately, none of the desired products was observed, and no reaction occurred.

Some control experiments were performed to obtain mechanistic insight into this cascade sequence (Scheme 3).

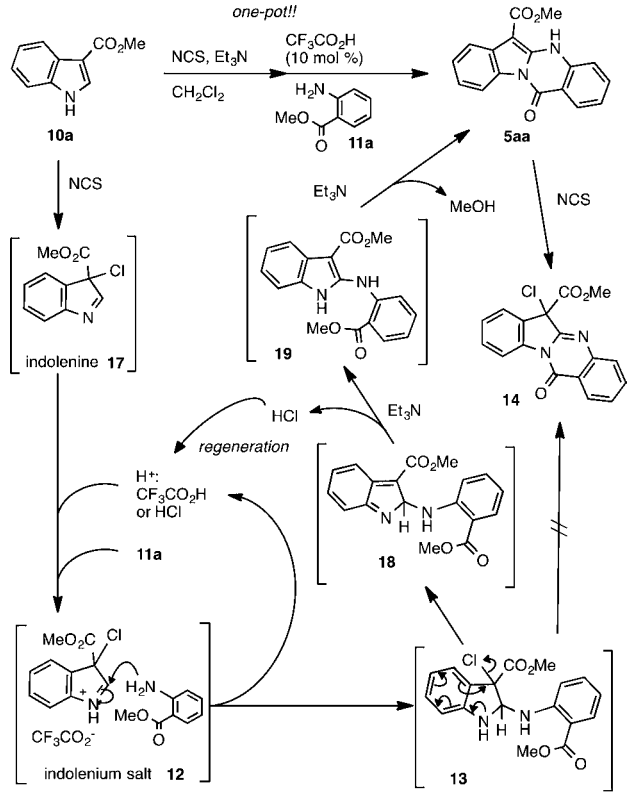
Scheme 3. Mechanistic Studies and Limitations



No product was obtained when NCS was not used, while the byproduct **14** was obtained as the sole product without the use of TFA or Et_3N (Scheme 3a). No reaction occurred without the use of both of Et_3N and TFA. After its formation, **5aa** would be further transformed into **14** by NCS because of delay in the cascade under the conditions. Furthermore, excess NCS resulted in lower yields due to generation of **14** as a byproduct (Scheme 3b). Then, we investigated the reaction between NCS and phaitanthrin E (Scheme 3c). Only **14** could be isolated in 88% yield. This means that **14** is not involved in the catalytic reaction cycle but is derived from the final compound **5aa**. These results all suggest that the combined use of NCS, TFA, and Et_3N is necessary to operate this transformation and inhibit the formation of **14**. In Scheme 2, uncyclized intermediate **15** was isolated in 70% yield along with **5ac** in 8% yield. When Et_3N or K_2CO_3 was used as a base, isolated intermediate **15** could be cyclized (Scheme 3d). When substrate **16** was used, base could promote the cyclization. The results in Scheme 3d suggest that the cyclization step is also the key step in the cascade sequence. Finally, some limitations of the cascade were found (Scheme 3e). In a preliminary experiment, unsubstituted indole **10g** and 3-substituted indoles **10h**–**j** were subjected to the standard reaction conditions. However, these reactions produced neither **5** nor 2-aminated products, while only complex mixtures were obtained. These results suggest that an ester group at C-3 of the indole is important in the bond-forming processes of the initial amination and cyclization in the cascade. This may be a reason that this type of one-pot intermolecular amination/cyclization reaction has not been realized until now.

A plausible reaction pathway for this cascade sequence based on the mechanistic investigation and literature precedents[15−18] is depicted in Scheme 4. At first, dearomatization of **10a** by

Scheme 4. Plausible Reaction Pathway



NCS affords chloroindolenine **17**.[15] Upon protonation by TFA, **17** is converted to chloroindolenium salt **12**,[16] which could increase the electrophilicity of C-2 of the indole ring.[17] The 2-position of **12** is attacked by the anthranilic nitrogen, affording C-2-aminated intermediate **13**. Subsequently, aromatization occurs via intermediate **18** with the release of HCl assisted by Et_3N[18] to afford **19** and regenerate the acid catalyst. Finally,

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nucleophilic attack of the indole nitrogen on the carbonyl moiety gives **5aa** with the release of MeOH. In the presence of excess NCS, **5aa** is converted to the undesired product **14**.

In conclusion, we have developed a novel acid-catalyzed amination/cyclization cascade under mild conditions. Phaitanthrin E derivatives were obtained in good yields from simple starting materials, and the reaction exhibits good functional group tolerance and scalability. The cascade proceeds through chlorine-mediated dearomatization/acid-catalyzed protonation of indolenine/C-2 amination/base-promoted aromatization and cyclization in a one-pot manner.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b03466.

Synthesis procedures and spectral and characterization data, including ^{1}H and ^{13}C NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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